IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

DECLARATION OF ACCURACY OF TRANSLATION
IN LIEU OF SWORN TRANSLATION (37 C.F.R. 1.55 & 1.68)

The undersigned traslator, having an office at

c/o Patent Department, Sankyo Co., Ltd., No. 2-58, 1-chome, Hiromachi, Shinagawa-ku, Tokyo, Japan

certifies and declares that:

(1) I am fully conversant both with the Japanese and English languages.

(2) (A) I have translated into English Japanese Patent Application Number filed .
A copy of said English translation is attached hereto.

(2) (B) I have carefully compared the attached English-language translation of Japanese Patent Application Number 89116/1981 filed June 10, 1981 , with the original Japanese-language patent application.

(3) The translation is, to the best of my knowledge, and belief, and accurate translation from the original into the English language.

The undersigned declares further that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the matter with which this translation is used.

Date: February 18, 1983

Akio Ohno

English Translation
of Certified Copy

PATENT OFFICE

JAPANESE GOVERNMENT

This is to certify that the annexed is a true copy of the following application as filed with this Office.

Date of Application : June 10, 1981

Application Number : Patent Application No. 89116/1981

Applicant : Sankyo Company, Limited

Director-General, HARUKI SHIMADA

Patent Office

Official Seal

Certificate Serial No. 25308

Application for Patent (Patent Application pursuant to a proviso of Article 38 in Patent Law)

June 10, 1981

(6,300 yen)

To : Haruki Shimada, Director-General of the Patent Office

1. Title of Invention :

Cephalosporin derivatives and process for preparing thereof

2. Number of Inventions described in claim : 6

3. Inventor

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6. List of appended documents

(1) Specification	1 copy
(2) Drawings	None
(3) Power of Attorney	1 copy
(4) Duplicate of Application	1 copy

7. Other Inventor, Patent Applicant or Attorney in addition to the foregoing person

(1) Inventor

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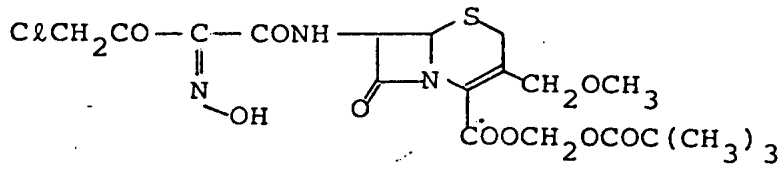
S P E C I F I C A T I O N

1. Title of the Invention

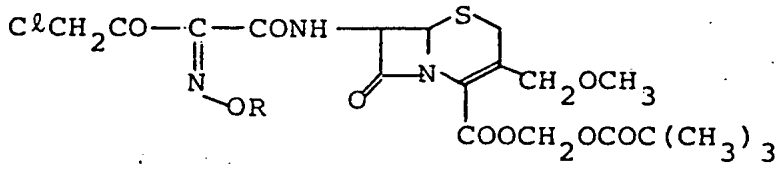
Cephalosporin derivatives and process for preparing thereof

2. Scope of Patent Claim

(1) A cephalosporin derivative having the formula

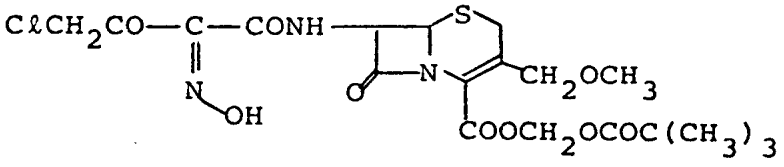


(2) A cephalosporin derivative having the formula

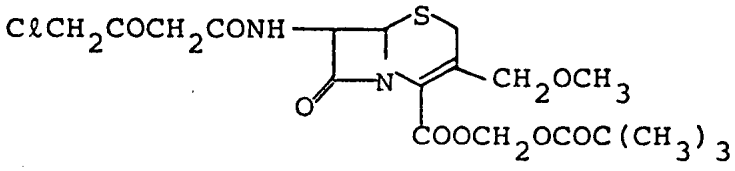


(wherein R represents a lower alkyl group)

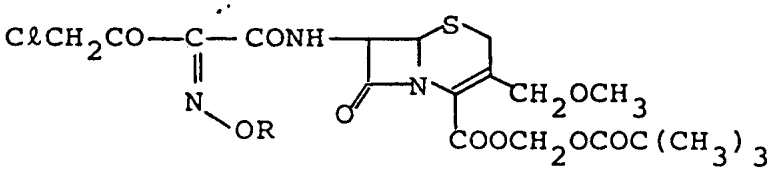
(3) A process for preparing a cephalosporin derivative having the formula



which comprises nitrosoating a compound having the formula

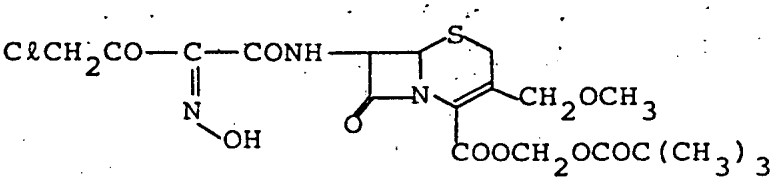


(4) A process for preparing a cephalosporin derivative having the formula

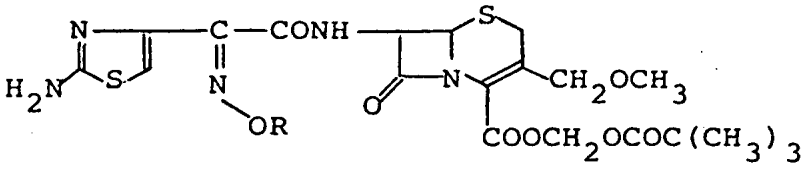


(wherein R represents a lower alkyl group)

which comprises alkylating a compound having the formula

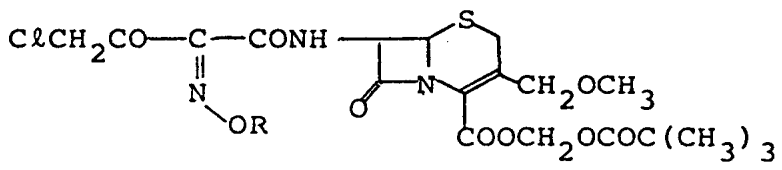


(5) A process for preparing a cephalosporin derivative having the formula



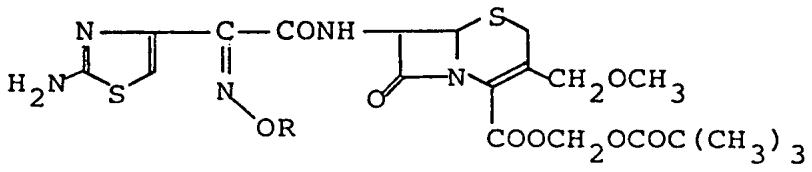
(wherein R represents a lower alkyl group)

which comprises reacting a compound having the formula

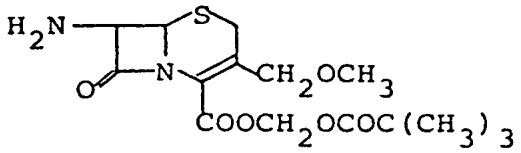


(wherein R represents a lower alkyl group)
with thiourea.

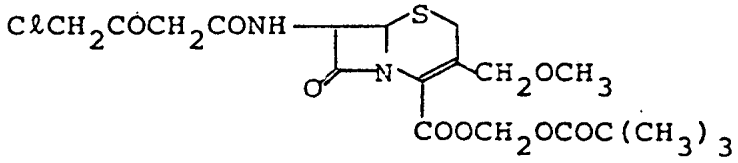
(6) A process for preparing a cephalosporin derivative having the formula



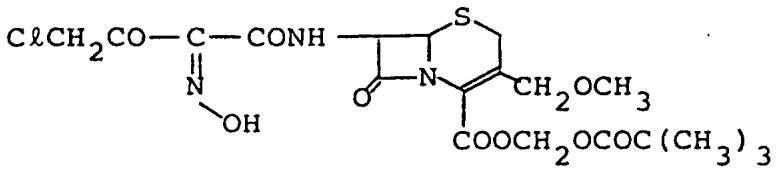
(wherein R represents a lower alkyl group)
which comprises acylating a compound having the formula



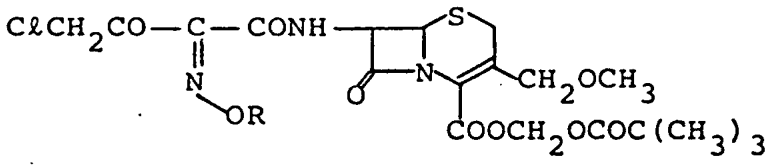
with 4-chloro-3-oxobutyryl chloride to give a compound having the formula



nitrosoating the latter compound to give a compound having the formula



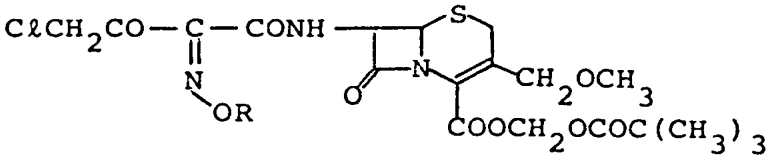
alkylating the latter compound to give a compound having the formula



(wherein R represents a lower alkyl group)
and reacting the latter compound with thiourea.

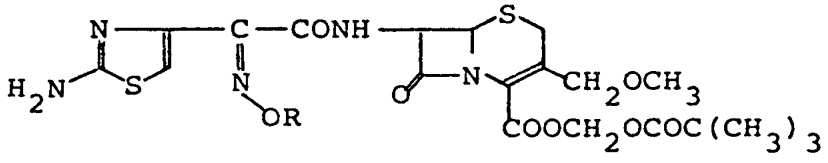
3. Detailed description of the Invention

This invention relates to cephalosporin derivatives having the formula



(I)

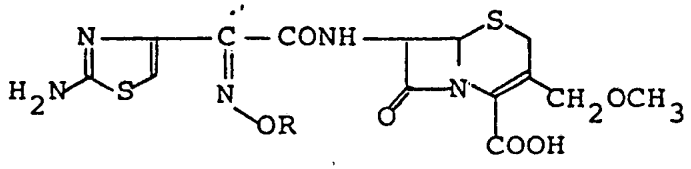
(wherein R represents a lower alkyl group)
and intermediates the synthesis thereof and processes for preparing them, and further relates to a process for preparing cephalosporin derivatives having the formula



(II)

(wherein R represents a lower alkyl group)
which comprises reacting the above compound (I) with thiourea.

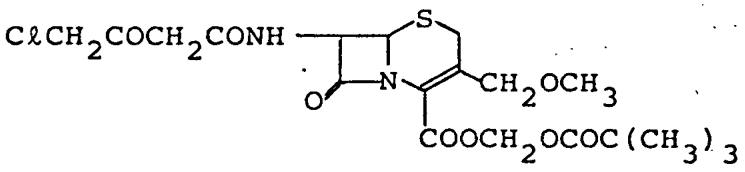
The present inventors have formerly found that a novel cephalosporin derivative having the formula (II) is readily absorbed from digestive tracts when administered orally and, after absorption, hydrolyzed at its pivaloyl oxymethyl ester moiety to produce a novel cephalosporin having the formula



(III)

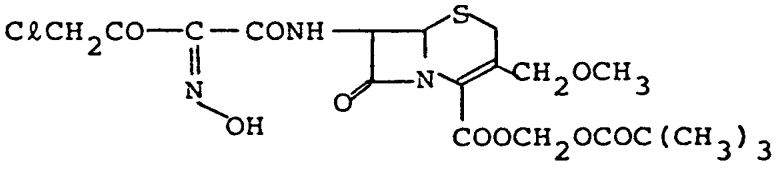
(wherein R represents a lower alkyl group)
which has potent anti-bacterial activities, and that it is useful as cephalosporin preparations for oral administration (Japanese Patent Application No. 136449/80).

As a result of earnest investigation on the process for preparing the cephalosporin derivatives having the formula (II), the present inventors have now found that the aimed compounds (II) can be prepared by nitrosoating a novel cephalosporin derivative having the formula



(IV)

to give a compound having the formula



(V)

alkylating the latter compound to give the compound having the formula (I) and reacting the latter compound with thiourea, and completed the present invention.

In the above formulae (I) and (II), R represents a straight or branched alkyl group having from 1 to 4 carbon atoms such as methyl, ethyl, propyl, isopropyl, butyl or isobutyl, but especially preferable group is methyl or ethyl group.

The reactions of the invention are illustrated below.

The starting compound (IV) can be prepared by acylating pivaloyloxymethyl 7-amino-3-methoxymethyl-3-cephem-4-carboxylate with 4-chloro-3-oxobutyryl chloride obtained by reacting diketene with chlorine. The acylation is usually conducted in a solvent by conventional means. The solvent is not limited as far as it does not obstruct the reaction and exemplified by methylene chloride, chloroform, tetrahydrofuran and dioxane. The acylation is preferably conducted in the presence of a base. As the base employed, there may be mentioned an organic base such as triethylamine, pyridine, dimethylaniline and diethylaniline. The reaction is completed at around room temperature or below within from several minutes to several hours. After completion of the reaction, the product (IV) may be recovered and purified by conventional means, for example, concentration, extraction with organic solvents, chromatographic techniques and recrystallization.

The nitrosoation of the compound (IV) to prepare the compound (V) is known as nitrosoation of a reactive methylene group and conducted by reacting the starting compound with a metal salt of nitrous acid under acidic condition, or with an ester of nitrous acid under suitable conditions. In case of the compound of this invention, however, it is necessary to carry out the reaction under such a condition that the cephalosporin moiety and the chlorine atom in the side chain at the 7-position do not participate in the reaction. It is accordingly desirable to carry out the reaction from weakly acidic to weakly basic conditions below room temperature.

The reaction is usually carried out in the presence of a solvent. The solvent is not limited as far as it is capable of dissolving the starting compound (IV) and does not obstruct the reaction. Examples of such solvents include formic acid, acetic acid, tetrahydrofuran, methanol, ethanol, chloroform, ethyl acetate and benzene and mixtures of water with said solvents. A suitable solvent is selected from those solvents depending on a kind of the nitrosoating agent.

Examples of the metal salt of nitrous acid employed as the nitrosoating agent include an alkali metal salt of nitrous acid such as sodium nitrite or potassium nitrite, preferably sodium nitrite. As the nitrous acid ester, there may be employed an ester with a lower alcohol, for example,

amyl nitrite and butyl nitrite.

In case where the nitrous acid metal salt is used as the nitrosoating agent, the reaction is necessary to be carried out under acidic condition. If an acidic solvent such as formic acid or acetic acid is not employed, addition of an organic or inorganic acid is necessary. Use of formic acid or acetic acid, accordingly, is preferable.

The reaction is carried out at around room temperature or below and completed within from several minutes to several hours.

After completion of the reaction, the product (V) may be isolated and purified by conventional means, for example, concentration, extraction with organic solvents and chromatographic techniques. The alkylation of the compound (V) to prepare the compound (I) is partially an alkylation of oxime and carried out by reacting the starting compound with a suitable alkylating agent.

The solvent is not limited as far as it does not obstruct the reaction. Examples of the solvent include acetone, tetrahydrofuran, dioxane, methanol, ethanol, chloroform, ethyl acetate, ether and N,N-dimethylformamide and a mixture of these solvents.

As the alkylating agent, there may be mentioned, for example, dimethyl sulfate, diethyl sulfate, diazomethane and a halogenated alkyl such as methyl iodide or ethyl iodide.

The reaction is carried out in the presence of a base, for example, alkali metal carbonates such as sodium carbonate or potassium carbonate, alkali metal hydroxides such as sodium hydroxide or potassium hydroxide, triethylamine, pyridine and dimethylaniline, except when diazoalkanes such as diazomethane are used.

The reaction is usually completed at room temperature or below within from several minutes to several hours. After completion of the reaction, the product (I) may be isolated and purified by conventional means, for example, concentration, extraction with organic solvents, chromatographic techniques and recrystallization.

The reaction of the compound (I) with thiourea to prepare the compound (II) is partially the synthesis of an aminothiazole derivative by reacting the haloketone with thiourea.

The reaction, also is usually carried out in the presence of a solvent. The solvent is not limited as far as it does not obstruct the reaction. There may be usually employed organic solvents, for example, N,N-dimethylformamide, N,N-dimethylacetamide, methanol, ethanol and tetrahydrofuran and a mixture of water with these organic solvents.

The reaction is usually completed at around room temperature within from 1 to 10 hours. Thiourea is used in an amount of 1 to several equivalents to the compound (I).

In order to accelerate the reaction, it is effective to add a suitable amount of sodium iodide and to neutralize formed hydrogen chloride by addition of a neutral phosphate buffer solution.

The reaction product (II) may be isolated and purified by conventional means, for example, concentration, extraction with organic solvents, chromatographic techniques, reprecipitation and recrystallization.

The process for preparing the present compounds is more concretely illustrated by the following Referential Examples and Examples, but they are not to be construed as limitating the scope of this invention.

Referential Example 1

Preparation of pivaloyloxymethyl 7-amino-3-methoxymethyl-3-cephem-4-carboxylate p-toluenesulfonic acid salt

A) In 90 mℓ. of N,N-dimethylacetamide was dissolved 38 g. of 7-phenoxyacetamido-3-methoxymethyl-3-cephem-4-carboxylic acid and, after cooling to -10 °C., 18 g. of dicyclohexylamine was added thereto.

To the mixture was added 30 g. of iodomethyl pivalate, followed by stirring at 5 °C. for an hour.

To the reaction mixture was added 200 mℓ. of ethyl acetate and insolubles were filtered off. The filtrate was washed successively with 60 mℓ. of a 5% hydrochloric acid

solution (twice), water, a 5% aqueous sodium bicarbonate solution, a saturated aqueous potassium bicarbonate solution and an aqueous sodium chloride solution, dried over magnesium sulfate and concentrated. The residue was chromatographed through silica gel eluted with n-hexane - ethyl acetate (1 : 1) to give 40 g. of pivaloyloxymethyl 7-phenoxyacetamido-3-methoxymethyl-3-cephem-4-carboxylate as a slightly yellow powder.

NMR spectrum ($CDC\ell_3$) δ ppm

1.25 (9H, s, $(CH_3)_3C$)

3.35 (3H, s, OCH_3)

3.54 (2H, s, CH_2 at 2-position)

4.29 (2H, s, CH_2 at 3-position)

4.58 (2H, s, $PhO\underline{CH_2}$-)

5.01 (1H, d, J = 5 Hz, H at 6-position)

5.6 - 6.1 (3H, m, at 7-position and $COO\underline{CH_2}O$-)

6.7 - 7.6 (6H, m, Phenyl and NH)

B) In 310 mℓ. of dry methylene chloride was dissolved 31 g. of pivaloyloxymethyl 7-phenoxyacetamido-3-methoxymethyl-3-cephem-4-carboxylate. To the solution was added 12.7 mℓ. of pyridine, followed by cooling to -50 °C. 26 g. of phosphorus pentachloride was added to the mixture and cooling was stopped. The mixture was stirred for an hour to obtain a brown solution. The mixture was again cooled to -50 °C. and 100 mℓ. of methanol was added slowly thereto. After completion of the addition, the mixture was stirred at around

-10 °C. for 30 minutes and neutralized by addition of a saturated aqueous sodium bicarbonate solution at around 0 °C. The methylene chloride layer was separated and the aqueous layer was extracted once with methylene chloride. The extract was combined with the methylene chloride layer which was separated above. The combined solution was dried over magnesium sulfate and concentrated under reduced pressure. The pyridine remained in the residue was separated by azeotropic distillation, twice with toluene and twice with ethyl acetate. The residue obtained was dissolved in 200 mℓ. of ethyl acetate. To the solution was added a solution of 12 g. of p-toluenesulfonic acid monohydrate in 100 mℓ. of ethyl acetate. The mixture was left to stand overnight in a refrigerator. The produced crystals were collected on a filter, washed with ethyl acetate and dried to afford 24 g. of pivaloyloxymethyl 7-amino-3-methoxymethyl-3-cephem-4-carboxylate p-toluenesulfonic acid salt as cotton-like, colourless needles, which were gradually coloured at around 160 °C. and decomposed at around 177 °C.

Elementary analysis

Calculated for $C_{15}H_{27}N_2O_6S \cdot C_7H_8O_3S$: C, 49.80; H, 5.70; N, 5.28; S, 12.08

Found : C, 49.76; H, 5.60; N, 5.00; S, 12.06

Example 1

Preparation of pivaloyloxymethyl 7-(4-chloro-3-oxobutyryl-amino)-3-methoxymethyl-3-cephem-4-carboxylate

In 10 mℓ. of dry methylene chloride was dissolved 725 mg. of diketene, followed by stirring at -20 °C. To the solution was added dropwise 30 mℓ. of a carbon tetrachloride solution containing 620 mg. of chlorine to produce 4-chloro-3-oxobutyryl chloride. On the other hand, 2 g. of pivaloyloxymethyl 7-amino-3-methoxymethyl-3-cephem-4-carboxylate p-toluenesulfonic acid salt and 1.16 mℓ. of diethylaniline were dissolved in 20 mℓ. of methylene chloride. The resulting solution was cooled to -10 °C. and the 4-chloro-3-oxobutyryl chloride solution obtained above was added dropwise thereto. The mixture was stirred at that temperature for 30 minutes and concentrated under reduced pressure. The resulting residue was dissolved in 50 mℓ. of ethyl acetate, washed successively with water, a 5% hydrochloric acid and an aqueous sodium chloride solution, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was dissolved in 3 mℓ. of methylene chloride and 30 mℓ. of ether was added thereto, followed by being left to stand. The produced needles were collected on a filter, washed with ether and dried to give 1.47 g. of the titled compound. m.p. 131.5 - 132.5 °C.

NMR spectrum ($CDC\ell_3$) δ ppm

1.23 (9H, s)

3.31 (3H, s, OCH_3)

3.54 (2H, s, at 2-position)

3.65 (2H, s, CH_2)

4.26 (2H, s, CH_2)

4.29 (2H, s, CH_2)

4.97 (1H, d, J = 5.5 Hz, at 6-position)

5.65 - 6.0 (3H, m, at 7-position and CH_2)

7.64 (1H, d, J = 9 Hz)

Example 2

Preparation of pivaloyloxymethyl 7-(4-chloro-3-oxo-2-hydroxyiminobutyrylamino)-3-methoxymethyl-3-cephem-4-carboxylate

In 25 mℓ. of acetic acid was dissolved 2.57 g. of pivaloyloxymethyl 7-(4-chloro-3-oxobutyrylamino)-3-methoxymethyl-3-cephem-4-carboxylate. To the solution was added slowly 409 mg. of sodium nitrite at room temperature, followed by stirring for 30 minutes. The reaction mixture was diluted with 200 mℓ. of ethyl acetate, washed three times with a saturated aqueous sodium chloride solution, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was subjected twice to azeotropic distillation using toluene. The resulting residue was dried to afford 2.7 g. of the titled compound as a foamy solid.

NMR spectrum ($CDC\ell_3$) δ ppm

1.23 (9H, s)

3.33 (3H, s, OCH_3)

3.59 (2H, s, CH_2 at 2-position)

4.33 (2H, s, CH_2 at 3-position)

4.75 (2H, s, CH_2)

5.05 (1H, d, J = 5.5 Hz, at 6-position)

5.6 - 6.1 (3H, m, at 7-position and CH_2)

9.3 (1H, d, J = 9 Hz)

Example 3

Preparation of pivaloyloxymethyl 7-(4-chloro-3-oxo-2-(Z)-methoxyiminobutyrylamino)-3-methoxymethyl-3-cephem-4-carboxylate

In 40 mℓ. of tetrahydrofuran was dissolved 5 g. of pivaloyloxymethyl 7-(4-chloro-3-oxo-2-hydroxyiminobutyryl-amino)-3-methoxymethyl-3-cephem-4-carboxylate. To the resulting solution was added a solution of 2 g. of sodium carbonate in 40 mℓ. of water. 5 g. of dimethyl sulfate was added to the above mixture, followed by stirring for 30 minutes. The reaction mixture was diluted with 150 mℓ. of ethyl acetate, washed twice successively with a saturated aqueous sodium bicarbonate solution and a saturated aqueous potassium bisulfate solution each, dried over anhydrous magnesium sulfate and concentrated under reduced

pressure. The residue was chromatographed through 100 g. of silica gel eluted with a mixed solvent of chloroform and ethyl acetate (3 : 1) to give a solid containing the titled compound. The solid was dissolved in 30 mℓ. of ether and left to stand under ice-cooling to produce crystals, which were washed with ether and dried to afford 1.9 g. of the titled compound as needles. m.p. 168.5 - 169.5 °C.

NMR spectrum ($CDC\ell_3$) δ ppm

1.24 (9H, s)

3.33 (3H, s, OCH_3)

3.57 (2H, s, CH_2 at 2-position)

4.19 (3H, s, OCH_3)

4.30 (2H, s, CH_2 at 3-position)

4.60 (2H, s, CH_2)

5.03 (1H, d, J = 5.5 Hz, at 6-position)

5.6 - 6.1 (3H, m, CH_2 and 7-position)

7.19 (1H, d, J = 9H, NH)

Example 4

Preparation of pivaloyloxymethyl 7-[2-(2-aminothiazol-4-yl)-2-(Z)-methoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylate

In 5 mℓ. of dimethylacetamide was dissolved 47 mg. of pivaloyloxymethyl 7-(4-chloro-3-oxo-2-(Z)-methoxyimino-butyrylamino)-3-methoxymethyl-3-cephem-4-carboxylate. 14 mg.

of thiourea was added to the solution obtained above, followed by stirring at room temperature for 4 hours. The reaction mixture was diluted with 50 mℓ. of ethyl acetate, washed three times with 15 mℓ. of water each, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The resulting residue was dissolved in 1 mℓ. of chloroform and 20 mℓ. of isopropyl ether was added thereto. Produced precipitates were collected on a filter and dried to afford 50 mg. of the titled compound as a colourless powder.

NMR spectrum ($CDC\ell_3$) δ ppm

1.22 (9H, s)

3.30 (3H, s, OCH_3)

3.53 (2H, s, CH_2 at 2-position)

4.00 (3H, s, OCH_3)

4.30 (2H, s, CH_2 at 3-position)

5.05 (1H, d, J = 5.0 Hz, at 6-position)

5.7 - 6.3 (5H, m, NH_2 at 7 position, and NH_2 and CH_2)

6.63 (1H, s)

8.27 (1H, d, J = 9 Hz, NH)

Example 5

Preparation of pivaloyloxymethyl 7-(4-chloro-3-oxo-2-(Z)-ethoxyiminobutyrylamino)-3-methoxymethyl-3-cephem-4-carboxylate

In 5 mℓ. of tetrahydrofuran was dissolved 505 mg. of

pivaloyloxymethyl 7-(4-chloro-3-oxo-2-hydroxyiminobutyryl-amino)-3-methoxymethyl-3-cephem-4-carboxylate. To the resulting solution was added a solution of 106 mg. of sodium carbonate in 5 mℓ. of water. The mixture was treated with 308 mg. of diethyl sulfate for an hour and post-treated and chromatographed in the same procedure as in Example 3 to obtain 96 mg. of a solid containing the titled compound. The solid was dissolved in ether, followed by being left to stand under ice-cooling. Produced precipitates were collected on a filter, washed with ether and dried to give 57 mg. of the titled compound as needles. m.p. 171 - 172 °C.

NMR spectrum ($CDC\ell_3$) δ ppm

1.23 (9H, s)

1.39 (3H, t, J = 7 Hz)

3.35 (3H, s, OCH_3)

3.57 (2H, s, CH_2 at 2-position)

4.32 (2H, s, CH_2 at 3-position)

4.43 (2H, q, J = 7 Hz)

4.60 (2H, s, CH_2)

5.04 (1H, d, J = 5.5 Hz, at 6-position)

5.6 - 6.1 (3H, m, CH_2 and at 7-position)

7.17 (1H, d, J = 9 Hz, NH)

Example 6

Preparation of pivaloyloxymethyl 7-[2-(2-aminothiazol-4-yl)-2-(Z)-ethoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylate

In 6 mℓ. of dimethylacetamide was dissolved 57 mg. of pivaloyloxymethyl 7-(4-chloro-3-oxo-2-(Z)-ethoxyiminobutyryl-amino)-3-methoxymethyl-3-cephem-4-carboxylate. To the resulting solution was added 17 mg. of thiourea and the mixture was treated in the same procedure as in Example 4 to afford 63 mg. of the titled compound as a colourless powder.

NMR spectrum ($CDC\ell_3$) δ ppm

1.22 (9H, s, $C(CH_3)_3$)

1.31 (3H, t, $OCH_2\underline{CH_3}$)

3.30 (3H, s, OCH_3)

3.53 (2H, s, CH_2 at 2-position)

4.28 (2H, q, $O\underline{CH_2}CH_3$)

4.30 (2H, s, CH_2 at 3-position)

5.01 (1H, d, J = 5 Hz, H at 6-position)

5.7 - 6.2 (5H, m, H at 7-position, NH_2 and $COOCH_2O$-)

6.76 (1H, s, H at 5-position of thiazole)

7.70 (1H, d, J = 9 Hz, CONH)

Example 7

<u>Preparation of pivaloyloxymethyl 7-[2-(2-aminothiazol-4-yl)-2-(Z)-methoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylate</u>

In 1 mℓ. of N,N-dimethylacetamide was dissolved 100 mg. of pivaloyloxymethyl 7-(4-chloro-3-oxo-2-(Z)-methoxyimino-butyrylamino)-3-methoxymethyl-3-cephem-4-carboxylate. To

the resulting solution was added 86 mg. of sodium iodide, followed by stirring at room temperature for 15 minutes. To the mixture were added 15 mg. of thiourea and 1 mℓ. of a neutral phosphate buffer solution of pH 6.86 (KH_2PO_4 - Na_2HPO_4), followed by stirring for 3 hours. The reaction mixture was diluted with 20 mℓ. of ethyl acetate, washed successively with a 5% aqueous sodium thiosulfate solution, water, an aqueous sodium chloride solution, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The resulting residue was dissolved in 1 mℓ. of chloroform. 20 mℓ. of isopropyl ether was added to the solution to produce precipitates, which were collected on a filter and dried to afford 100 mg. of the titled compound as a colourless amorphous powder. Physical properties of the product thus obtained agreed with those of the product in Example 4.

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Following the procedure of Example 3, but replacing bromomethyl pivalate with 340 mg. of bromomethyl propionate, there was obtained 165 mg. of propionyloxymethyl 7-[2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylate as an almost colourless powder.

NMR ($CDCl_3$) δ ppm:

1.17 (3H, t, J = 6.5)

2.41 (2H, q, J = 6.5)

3.20 (3H, s)

3.35 (2H, ABq)

4.02 (3H, s)

4.17 (2H, s)

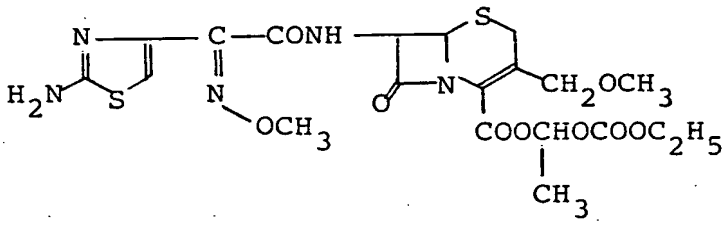
5.09 (1H, d, J = 5)

5.6 - 6.3 (5H, m)

6.68 (1H, s)

8.25 (1H, d, J = 9)

Example 6



Following the procedure of Example 3, but replacing bromomethyl pivalate with 600 mg. of α-ethoxycarbonyloxyethyl bromide (prepared by heating 600 mg of α-ethoxycarbonyloxy-

ethyl chloride and 800 mg. of sodium bromide in 3 mℓ. of acetonitrile for 10 hours), there was obtained 60 mg. of 1-ethoxycarbonyloxyethyl 7-[2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylate as a pale yellow powder.

NMR ($CDC\ell_3$) δ ppm

1.30 (3H, t, J = 7)

1.61 (3H, d, J = 5)

3.22 (3H, s)

3.42 (2H, ABq)

4.03 (3H, s)

4.15 (2H, s)

4.21 (2H, q, J = 7)

5.10 (1H, d, J = 5)

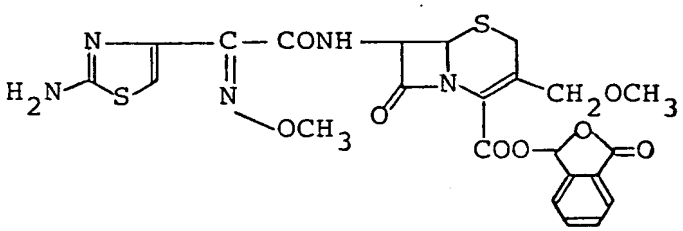
5.6 - 6.2 (3H, m)

6.70 (1H, s)

6.92 (1H, q)

8.20 (1H, d, J = 9)

Example 7



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(2) Isovaleryloxymethyl 7-[2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylate

(3) Pivaloyloxymethyl 7-[2-(2-aminothiazol-4-yl)-2-ethoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylate

(4) Pivaloyloxymethyl 7-[2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-ethoxymethyl-3-cephem-4-carboxylate

Example 10

2 mℓ. of an ether solution saturated with hydrogen chloride was added to a solution of 500 mg. of pivaloyloxymethyl 7-[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylate in 20 mℓ. of ethyl acetate. The reaction mixture was concentrated under reduced pressure to a volume of about 5 mℓ. and 20 mℓ. of diisopropyl ether was added thereto. Produced precipitates were collected on a filter, washed with diisopropyl ether and dried to afford 480 mg. of pivaloyloxymethyl 7-[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylate hydrochloride. Yield, 480 mg.

According to the above procedure, 500 mg. of pivaloyloxymethyl 7-[2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylate was treated

to give 470 mg. of its hydrochloride.

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